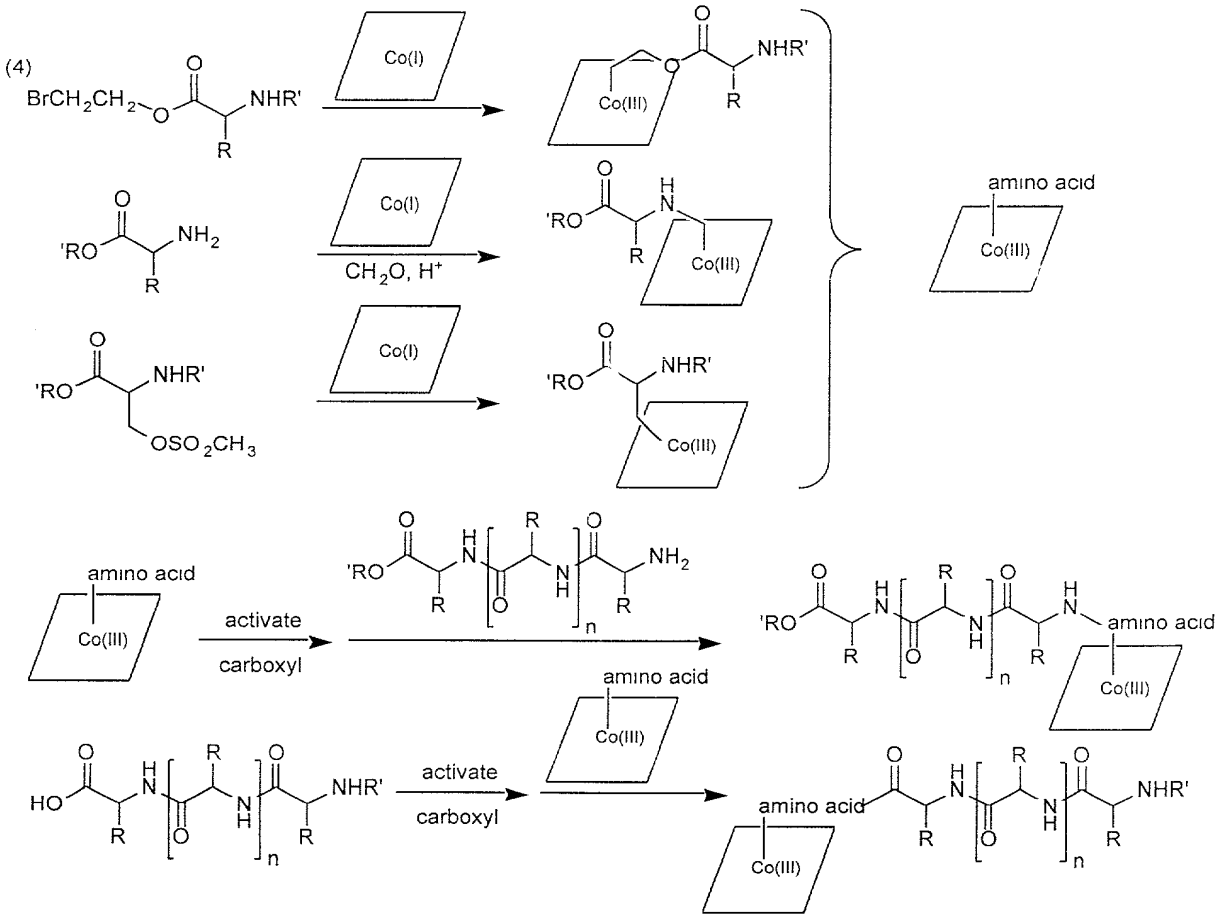
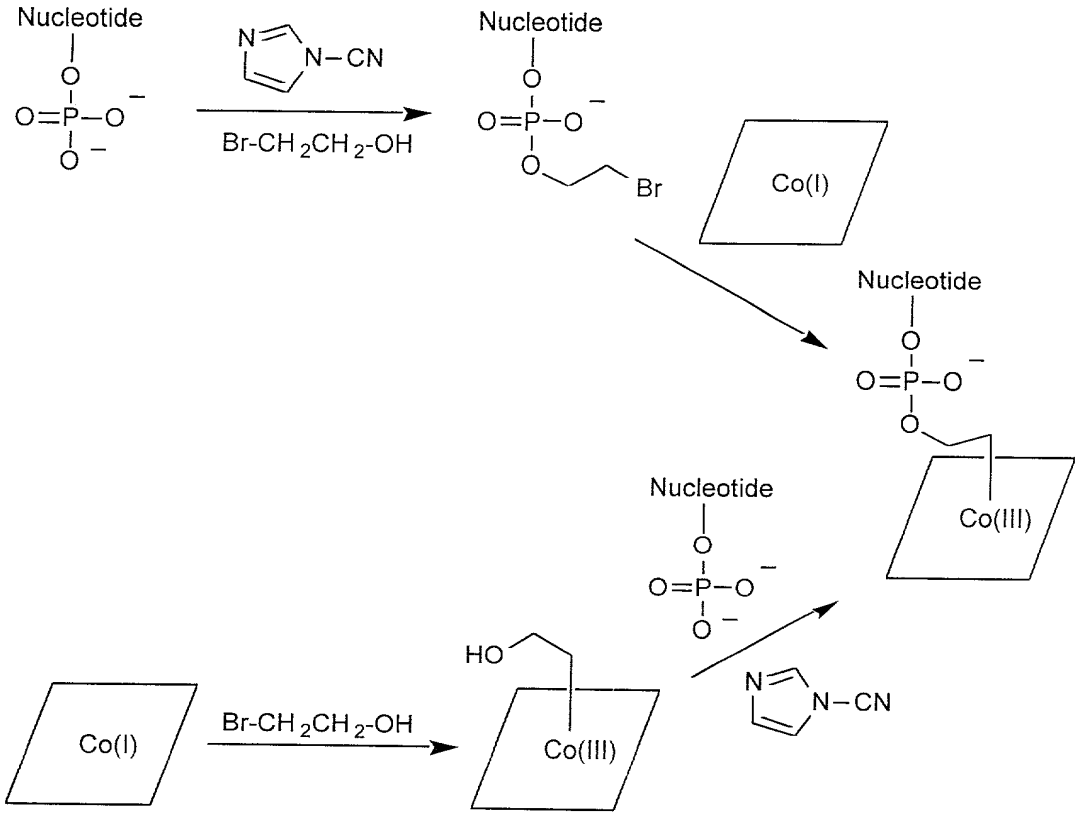


An oligonucleotide or nucleic acid containing bioconjugate can be synthesized by the following methods. In both methods, a phosphate ester is used to link the end of the nucleotide and a hydroxyethyl-Co group. This linkage can be accomplished by either directly coupling Co-CH_2CH_2-OH and Nucl-OPO_3^{2-} , or by esterifying Nucl-OPO_3^{2-} with Br-CH_2CH_2-OH, then displacing the Br with Co(I), as above.



An unsymmetrically substituted Co[SALEN] complex can be prepared from 5-amino-salicylaldehyde and the glycolate ether of 2,5-dihydroxybenzaldehyde. The amino group, which is prepared from commercially available 5-nitrosalicylaldehyde, functions as the attachment for the targeting molecule (binding domain, BD) by way of EDCI-catalyzed amide formation. The other molecule has a carboxylic acid unit attached for solubility enhancement. Coupling of these two molecules with ethylenediamine and Co(II) acetate furnishes a mixture of three complexes: the two symmetrical complexes and the mixed one. All of these are useful, although the one lacking a BD-unit attached to either side of the SALEN is less preferred.

With regard to binding domains, two possiblities are shown: a cobalamin derivative, and a peptide. In the former case, the known carboxylic acid is used to attach cobalamin to the amino group of the SALEN. This bioconjugate still usees cobalamin-based receptor-mediated endocytosis to get into the cell, but the drug is attached through the SALEN instead of the cobalamin. The latter case uses a peptide known to bind to cell surface receptors of tumor cells (e.g., a fragment of epidermal growth factor), with the carboxyl terminus attached to the amino group on the SALEN. Alternatively, one of the glutamate carboxyl groups of folate is used to

obtain a folate-based bioconjugate. In addition to connecting the binding domain via an amide linkage, one could use reductive amination if the targeting molecule contained an aldehyde (BD-CHO + SALEN-NH_2 + $NaBH_4$), or one could use the carboxyl group on the other piece to form an amide or ester linkage. Many other approaches (e.g., ether formation, olefination by Wittig reaction, attachment via a diester or diamide linker, etc.) are also possible.